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DOI:

[10.1017/S0033291717001386](https://doi.org/10.1017/S0033291717001386)

Document Version

Peer reviewed version

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Citation for published version (APA):

Rafferty, L. A., Cawkill, P., Stevelink, S., Greenberg, K., & Greenberg, N. (2018). Dementia, post-traumatic disorder and major depressive disorder: a review of the mental health risk factors for dementia in the military veteran population. *Psychological Medicine*. <https://doi.org/10.1017/S0033291717001386>

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Dementia, Post-Traumatic Stress Disorder and Major Depressive Disorder: A Review of the Mental Health Risk Factors for Dementia in the Military Veteran Population

L.A. Rafferty¹, P.E. Cawkill², S.A.M. Stevelink¹, K. Greenberg³, N. Greenberg¹

1 King's Centre for Military Health Research, King's College London, Weston Education Centre, Cutcombe Road, London SE5 9RJ, UK

2 Dstl (Defence Science & Technology Laboratory) Portsmouth West, Fareham, Hampshire, PO17 6AD, UK

3 March on Stress, Arena Business Park, 9 Nimrod Way Ferndown, Dorset, BH21 7UH, UK

Background: Dementia is currently incurable, irreversible and a major cause of disability for the world's older population. The association between mental health difficulties, such as Post Traumatic Stress Disorder (PTSD) and Major Depressive Disorder (MDD), and dementia has a long history within the civilian population. Despite the increased importance of this link within the military veteran population, who suffer a greater propensity of mental health difficulties and consist largely of over 65's, attention is only recently being paid to the salience of such an association for this group. This paper aims to explore the relationship between PTSD and MDD with dementia within the military veteran population.

Method: A systematic review was conducted on articles from 1990 to July 2016 on MEDLINE, EMBASE, EBSCO and Web of Science electronic databases with an update conducted in February 2017.

Results: Six empirical studies were identified from the review, the majority of which originated from the US. Five of the studies asserted that veterans with a diagnosis of either PTSD or MDD are at a significantly greater risk of developing dementia than 'healthy' controls. The final study, conducted in Australia, found only a small, but non-significant, correlation between earlier MDD and future dementia, but no concurrent correlation.

Conclusions: While causality cannot be determined, it is likely that PTSD and depressive disorders are related to an increased risk of dementia in military veterans. Potential pathological explanations and risk factors are reviewed and the clinical and neuroscience implications of these findings are explored.

Keywords: Post-Traumatic Stress Disorder; Major Depressive Disorder; Dementia; Military; Mental Health Disorders; Review; Veterans

1. Introduction

1.1 Dementia

Dementia is caused by degeneration of the brain and is characterised by symptoms such as memory loss, language difficulties and reduced problem solving ability (Alzheimer's Society, 2014). Dementia is irreversible and progressive meaning that symptoms continue to worsen throughout the patient's life (Alzheimer's Society, 2014). There are many types of dementia but this paper will focus on the four most common types. These along with the associated neuro-degenerative pathways are highlighted in Table One below (Alzheimer's Society, 2014, British Medical Journal, 2017a, b, c, d, NHS, 2015):

Table One: Neuro-degenerative Pathways to Dementia

| Dementia Label | Biological Pathway |
|--------------------------------|---|
| Alzheimer's Disease | Deposits of amyloid protein plaques and neurofibrillary tangles; brain atrophy; and neuronal degeneration |
| Vascular Dementia | A stroke or fatty deposits interrupt the blood supply to the brain interfering with the normal functioning; neuronal degeneration |
| Lewy Body Dementia | Deposits of proteins develop inside brain cells impacting neurotransmitters carrying messages between brain cells |
| Frontotemporal Dementia | Temporal and frontal lobe damage, typically caused by a genetic mutation, causing the neuronal degeneration |

Alzheimer's Disease is by far the most common form of dementia, estimated to account for up to 70% of dementia cases (World Health Organisation, 2015). According to the Alzheimer's Society (2014) rates of dementia in the U.K. general population are estimated to be around 850,000, affecting 1 in every 14 people over the age of 65. Age is the biggest risk factor for dementia with the risk doubling every 5 years after the age of 65 (Alzheimer's Society, 2014).

Dementia prevalence is increasing with the number of people living with dementia in the UK estimated to reach over 1 million by 2025, and over 2 million by 2050 (Lewis *et al.*, 2014). This increase comes at both a personal cost to people with dementia and their families and carers but also a huge economic cost to the UK. The current financial cost of dementia to the UK economy is over £24 billion a year, this is a combination of health and care costs and the vast contribution made by informal carers (Lewis *et al.*, 2014). We also know that people with dementia have a lower self-reported quality of life than both the general population as a whole and those over 65 (Lewis *et al.*, 2014).

1.2 MDD, PTSD and Dementia

The relationship between MDD and dementia has been discussed within the civilian literature for many years, according to Mahendra (1985) potentially back to the ninth century AD. A 2006 meta analyses within the civilian population suggests that for those with a diagnosis of MDD there is an Odds Ratio of between 2.03 (95% CI: 1.73 -2.38) and 1.90 (95% CI: 1.55 – 2.33) for dementia, depending on whether case control or cohort studies are examined (Ownby *et al.*, 2006). In addition to this, a recent review of the risk factors for dementia identified depression at any age, as well as late life depression, as two of the four core risk factors for dementia along with benzodiazepines use and frequency of social contact (Bellou *et al.*, 2017).

Whilst no comparable review exists exploring the relationship between PTSD and dementia within the civilian literature, empirical evidence is amassing which stresses the importance of this association across a range of populations. A study of 9/11 survivors found that current PTSD, as well as MDD diagnosis, was associated with a two fold increase in cognitive impairment (Clouston *et al.*, 2016). 12.8% of those screened displayed a level of cognitive impairment with 1.2% diagnosed with dementia, from a participant pool with an average age of only 53 these results are surprisingly high (Clouston *et al.*, 2016). Holocaust survivors with PTSD have been shown to demonstrate accelerated aging compared to both holocaust survivors without PTSD and 'healthy' controls (Golier *et al.*, 2002). A study exploring Swiss child labourers with PTSD indicated reduced cognitive function when compared to those without PTSD (Burri *et al.*, 2013).

1.2.1 Potential Pathways linking MDD/ PTSD and Dementia

Butters *et al.* (2008) and Greenberg *et al.* (2014) provide concise overviews of the potential pathways between MDD and PTSD (respectively) with dementia. The following section will

summarise the complimentary pathways discussed in these reviews, supplemented by evidence from the wider literature. It must be stressed that these are not the only potential pathways, but rather they represent a number of pathways commonly discussed in the literature. It is also worth highlighting that the pathways are not mutually exclusive.

1.2.1.1 Increased activation of the HPA

MDD, PTSD and dementia are associated with hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, and resultant increases in cortisol (Byers and Yaffe, 2014, Meziab *et al.*, 2014, Qureshi *et al.*, 2010, Veitch *et al.*, 2013, Weiner *et al.*, 2013, Yaffe *et al.*, 2010). Increases in cortisol are shown to impact cognitive ability at the time of release as well as lead to cognitive impairment in later life (Meziab *et al.*, 2014) with prolonged exposure to high levels of cortisol resulting in neuro-degeneration (Byers and Yaffe, 2014, Meziab *et al.*, 2014, Qureshi *et al.*, 2010, Veitch *et al.*, 2013, Weiner *et al.*, 2013, Yaffe *et al.*, 2010).

1.2.1.2 Increased cytokines and resultant inflammation

The HPA axis also controls the release of cytokines, proteins that impact certain neurotransmitters in the brain (Passmore, 2015). Increased levels of cytokines, seen in both MDD and PTSD, can cause inflammation which damages the brain and increases the risk of dementia (Byers and Yaffe, 2014, Veitch *et al.*, 2013, Yaffe *et al.*, 2010).

1.2.1.3 Increase in Amyloid Beta plaques

Amyloid Beta (A β) plaques are a diagnostic feature of Alzheimer's Dementia (Byers and Yaffe, 2014, Weiner *et al.*, 2013). Research indicates that MDD is also associated with an increase in A β deposition and that patients with both Alzheimer's Dementia and MDD have an increased rate of A β deposition than those with Alzheimer's Dementia alone (Byers and Yaffe, 2014, Veitch *et al.*, 2013). PTSD has also been proposed to be caused by alterations of hormones which control the production and deposition of A β plaques (Sibener *et al.*, 2014).

1.2.1.4 Cognitive reserve

The cognitive reserve theory states that PTSD and MDD may diminish cognitive reserve which may increase the risk, or speed up the process, of dementia (Apfel *et al.*, 2011, Qureshi *et al.*, 2010, Veitch *et al.*, 2013, Yaffe *et al.*, 2010). Higher levels of cognitive reserve, developed via factors such as higher socio economic status and educational attainment may 'protect' an individual from developing dementia (Dent *et al.*, 1998).

1.2.2 Potential Unifying Hypotheses

1.2.2.1 Inflammatory Neuro-degeneration

The theory of inflammatory neuro-degeneration is gaining traction as a potential explanation for the impacts of psychiatric conditions such as MDD and PTSD. This theory ties each of the above mechanisms together in a prospective 'unifying hypothesis'. When the body is exposed to stress it triggers an inflammatory response as a form of protection (Boorman *et al.*, 2015, Franklin *et al.*, 2015). Acute or prolonged stress can lead to increased inflammation and can result in neuro-degeneration (Boorman *et al.*, 2015, Franklin *et al.*, 2015). The inflammatory response is controlled by the HPA axis and involves an increase in pro-inflammatory cytokines which in turn activate microglia (Boorman *et al.*, 2015, Franklin *et al.*, 2015). Among other processes, microglia activation leads to an increase in release of NLRP3 and inhibition of Brain Derived Neuro-trophic Factor (BDNF) both of which can result in neuro-degeneration (Boorman *et al.*, 2015, Franklin *et al.*, 2015).

Dementia is characterised by neuro-degeneration and both lower levels of BDNF and higher levels of NLRP3, stimulated by increased levels of A β plaques, are found in dementia (Boorman *et al.*, 2015, Franklin *et al.*, 2015). This suggests that such inflammatory markers may represent the mediatory factor between MDD/ PTSD and dementia (Boorman *et al.*, 2015, Franklin *et al.*, 2015).

1.2.2.2 Brain reserve

Butters *et al.* (2008) describe the theory of brain reserve in relation to dementia. Brain reserve theory is based on the notion that individuals can tolerate more or less cell loss before clinical symptoms are observed, based on their level of cell redundancy. Indeed a meta-analysis by Valenzuela and Sachdev (2006) found that higher levels of brain reserve were associated with a lower risk of dementia, Odds Ratio: 0.54 (CI: 0.49-0.59). Butters *et al.* (2008) suggest that such a hypothesis may also act as a 'unifying hypothesis' for each of the mechanisms described above, whereby each leads to an increasing level of reduction in brain reserve and therefore an increasing risk of dementia.

In line with this theory Greenberg *et al.* (2014) highlight that it is important to remember that not everyone who is diagnosed with MDD or PTSD will develop dementia, rather it appears that conditions such as PTSD "play an ancillary role among numerous factors that are involved in pathogenesis of dementia" (pp. S163, Greenberg *et al.*, 2014). The next section will explore how military veterans may represent a population at an increased risk of the pathogenesis of dementia due to a number of additional such factors.

1.4 Increased Risk of Dementia for Military Veterans

1.4.1 Increased prevalence of MDD and PTSD

Common mental health disorders are reported to occur at an increased rate in military personnel compared to the general population. Indeed, within the UK (Goodwin *et al.*, 2015) found that the risk of common mental health disorders is approximately doubled in the military population as compared to the general population in employment (Odds Ratio of 1 versus an Odds Ratio of 2.4 respectively). Rates of PTSD are also reported at higher rates in military personnel from the US (12.6%) and Australia (8.3%) (Hunt *et al.* (2014). Although the rate of PTSD in the UK Armed Forces is approximate to that in the general population (~4%), when military personnel deployed in combat roles are singled out prevalence rates increase to 5.7% (Fear *et al.*, 2010). Therefore if, as civilian literature suggests, mental health conditions such as MDD and PTSD do represent risk factors for dementia, then military personnel, particularly those who have deployed, may represent a population with an increased vulnerability.

1.4.2 Substantial aging population

In addition to this, due to the influx of recruitment from World War II and National Service, 46% of the UK's veteran population is over the age of 75, compared to only 10% of the general population (Royal British Legion, 2014). As mentioned earlier, age is the most significant risk factor for dementia, illustrating a further heightened risk factor for the veteran community over the general population.

1.4.3 Metabolic syndrome

Metabolic syndrome is a combination of obesity, high blood pressure and diabetes. Both hypertension and diabetes are postulated to interfere with A β clearance (Yaffe *et al.*, 2014). As with obesity, although the prevalence of metabolic syndrome is not higher in the military population

when compared to the general population, the rate does increase in those in the military population with a mental health diagnosis (Yaffe *et al.*, 2014).

1.4.4 Physical inactivity

Physical activity is also described as a potential preventative factor for dementia since it both increases neuro-genesis, as well as decreasing the risk of vascular disease and reducing inflammation (Yaffe *et al.*, 2014). It has also been tentatively linked to lower levels of A β deposition in the brain (Yaffe *et al.*, 2014). Again, Yaffe *et al.* (2014) propose that although the rates of physical activity in the veteran population is similar to the general population, there is some evidence of 'retirement obesity' for veterans who have previously held high levels of physical activity that are suddenly reduced when transitioning out of the military.

1.4.5 Alcohol and Smoking

Alcohol and smoking are also identified as risk factors of dementia that are more common in the veteran population than the general population (Veitch *et al.*, 2013, Yaffe *et al.*, 2014). Smoking presents an increased risk of dementia in many ways including: vascular disease; inflammation; accelerated reductions in the cerebral blood flow; cerebral atrophy and the formation of white matter lesions and can roughly double the risk of Alzheimer's dementia (Veitch *et al.*, 2013). For alcohol, although a low intake may be protective against dementia, excessive alcohol intake can be neuro-toxic thus increasing the risk of dementia (Yaffe *et al.*, 2014).

1.4.6 Traumatic Brain Injury

One co-morbid condition that is frequently mentioned throughout the literature is Traumatic Brain Injury (TBI). TBI, is defined as "an external force to the head causes injury and results in alteration or loss of consciousness" (Sibener *et al.*, 2014) and is said to increase the risk of dementia by between a two and four fold rate (Sibener *et al.*, 2014). The rate of TBI is projected to be much higher in the military population compared to the general population due to the risk of TBI from Improvised Explosive Devices (IEDs) (Byers and Yaffe, 2014, Sibener *et al.*, 2014, Veitch *et al.*, 2013, Weiner *et al.*, 2013). Rates of TBI after the recent Iraq and Afghanistan conflicts are assessed to be around 7% in US troops, although rates as high as 22% have been proposed, compared to around 0.5% in the general US population (Veitch *et al.*, 2013). TBI has been proposed to interact with PTSD in three main ways: deposition of A β plaques and tau pathology; reduction in cognitive reserve; and ischemic lesions (Veitch *et al.*, 2013).

A link between mental health conditions such as MDD and PTSD with dementia holds a great deal of importance, especially for the veteran population who may be at an increased risk due the increased amplified prevalence of mental health problems as well as the heightened impact of a number of additional risk factors. This paper sets out to identify scientific literature examining the association between MDD, PTSD and dementia in the older veteran population.

2. Method

2.1 Search Strategy

Relevant articles were identified by performing searches of the bibliographic databases MEDLINE, EMBASE, EBSCO, Web of Science, and Google Scholar. Searches included keywords: Dementia, Alzheimer Disease, depression, anxiety, Post-Traumatic Stress Disorder (PTSD), common mental disorders, alcohol & drug misuse, stress, military personnel, armed forces, and veterans. Searches were limited to studies in articles published between 1990 and July 2016, in the English language,

exploring the relationship between dementia and mental health in military veterans'. The full search strategy can be found in Appendix One.

2.2 Selection Strategy

A total of 130 articles were retrieved from bibliographic searches. 39 papers were removed as duplicates and a further 13 were rejected after reviewing paper titles. Abstract reviews were then conducted on the remaining 78 papers, removing a further 53 as irrelevant. The final 25 papers were read in full, of which 5 papers were deemed to be relevant to the search criteria. Hand searching was also conducted of all references cited in articles. This process was conducted by LAR with a 10% sample of abstracts and full papers blind reviewed by SAMS with any discrepancies discussed and resolved. An updated search, following the same protocol, was conducted in February 2017 which identified an additional paper for inclusion. The inclusion process is outlined below in Figure One.

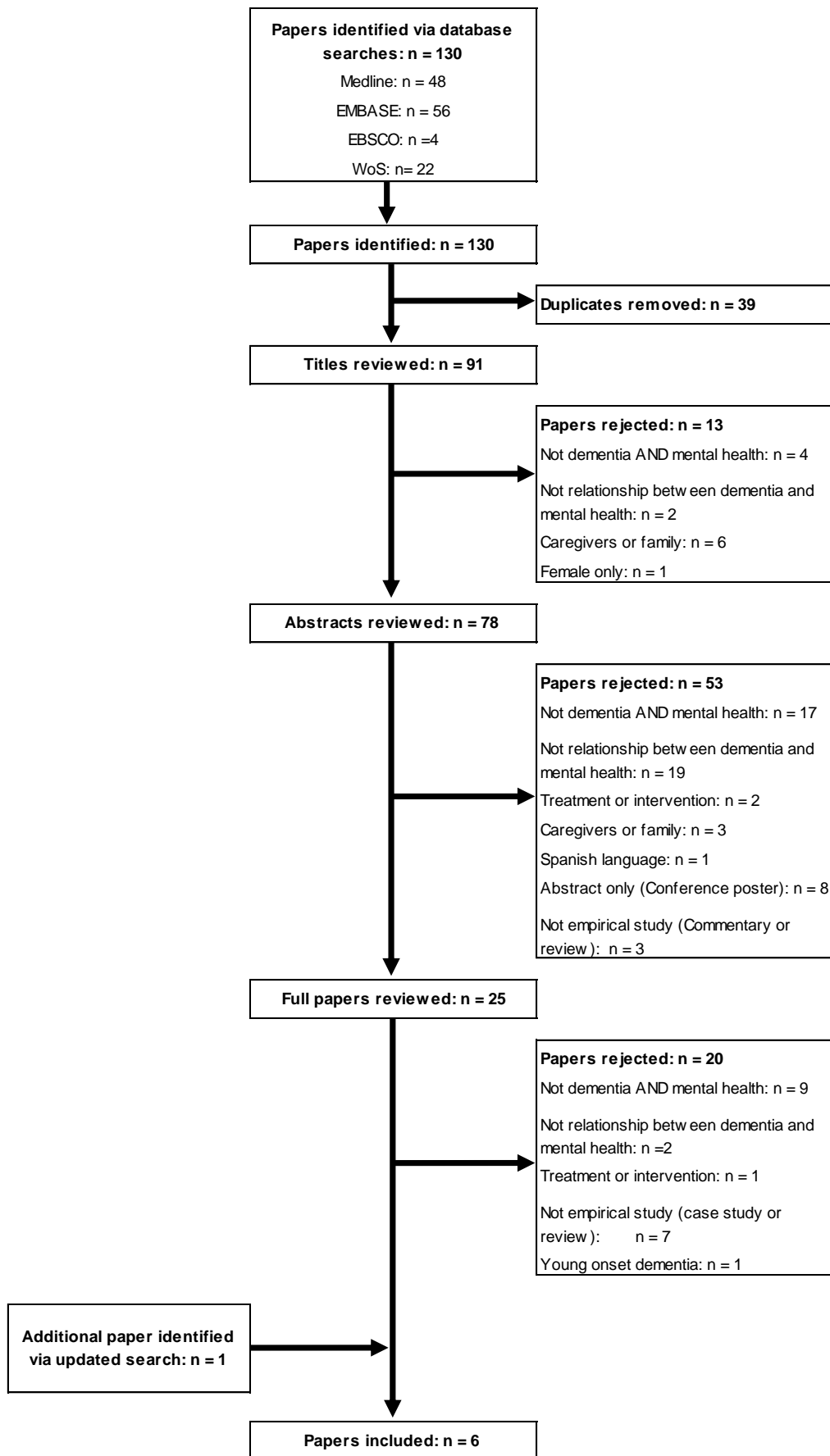


Figure One: Inclusion Process

2.3 Quality Appraisal

A quality criteria assessment tool for cohort studies was used to rate the methodological quality of the studies (<http://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools>). LAR and SAMS rated the studies independently according to the quality criteria given. Any discrepancies were discussed and resolved. After scoring all the criteria, the different ratings were listed and a final overall rating for each study was given jointly (Appendix Two).

2.4 Study Characteristics

Five of the papers included in this review were retrospective cohort studies based on data drawn from the Department of Veteran's Affairs medical care system in the US. The studies identified eligible participants either aged 55 and over (Byers *et al.*, 2012, Meziab *et al.*, 2014, Yaffe *et al.*, 2010), aged 56 and over (Mawanda *et al.*, 2017) or aged 65 and over (Qureshi *et al.*, 2010). Each of the studies utilised the existing definitions for dementia and mental health diagnosis, namely the ICD-9 Clinical Modification, with information about the diagnoses drawn from medical records. The remaining paper was conducted in Australia with randomly selected veterans from World War II taking part in a prospective cohort study, aged between 65 and 85 years at the second phase (Dent *et al.*, 1998). Depression and dementia were explored via a clinical interview, focused on the DSM criteria for MDD, and the DSM criteria for dementia, along with the Mini Mental State exam (Dent *et al.*, 1998). The number of study participants ranged from 209 (Dent *et al.*, 1998) to 417,172 (Mawanda *et al.*, 2017). All of the studies report that there were mental health diagnoses of either MDD or PTSD at a baseline point and then subsequent dementia diagnoses at a follow up point. Only the Australian study specifies that the diagnosis of PTSD/ MDD was still current at the follow up phase. Table Two below contains details of the characteristics of each paper reviewed and Table Three provides information on the dementia types explored within each study.

Table Two: Characteristics of Included Papers

| Author | Study Design | Sample | Size | Mental Health Classification | Mental Health Diagnosis | Mental Health Diagnosis Data Source | Association |
|-----------------------|----------------------------|---------------------|-------------|------------------------------|---|-------------------------------------|------------------------------|
| Byers et al. (2012) | Retrospective Cohort Study | US veterans | n = 281,540 | ICD-9 Clinical Modification | Major Depression Disorder | Department of Veteran's Affairs | HR: 2.18 (95% CI: 2.08-2.28) |
| | | 55 years & over | | | Dysthymia | | HR: 1.96 (95% CI: 1.71-2.25) |
| Dent et al. (1998) | Prospective Cohort Study | Australian veterans | n = 209 | DSM Criteria | Major Depressive Disorder/ Other Depression | Clinical Interview | R: 0.13 (95% CI: 0.00-0.26) |
| | | 56 years & over | | Zung Depression Scale | Depressive symptoms | | R: 0.16 (95% CI: 0.02-0.29) |
| Mawanda et al. (2017) | Retrospective Cohort Study | US veterans | n = 417,172 | ICD-9 Clinical Modification | PTSD | Department of Veteran's Affairs | HR: 1.35 (95% CI: 1.27-1.43) |
| | | | | | PTSD + Psychotropic Medication (SSRI) | | HR: 1.99 (95% CI: 1.72-2.29) |

| | | | | | | | |
|-----------------------|----------------------------|-----------------|-------------|-----------------------------|---------------------------------------|---------------------------------|------------------------------|
| | | | | | PTSD + Psychotropic Medication (SNRI) | | HR: 2.02 (95% CI: 1.78-2.30) |
| | | 56 years & over | | | PTSD + Psychotropic Medication (AAI) | | HR: 4.21 (95% CI: 3.72-4.76) |
| Meziab et al. (2014) | Retrospective Cohort Study | US veterans | n = 484 | ICD-9 Clinical Modification | PTSD | Department of Veteran's Affairs | HR: 1.52 (95% CI: 1.41-1.64) |
| | | 55 years & over | | | PTSD + POW | | HR: 2.24 (95% CI: 1.72-2.92) |
| Qureshi et al. (2010) | Retrospective Cohort Study | US veterans | n = 10,481 | ICD-9 Clinical Modification | PTSD | Department of Veteran's Affairs | OR: 2.2 (95% CI: 1.8-2.6) |
| | | 65 years & over | | | PTSD + Purple Heart | | OR: 1.4 (95% CI: 0.7-2.7) |
| Yaffe et al. (2010) | Retrospective Cohort Study | US veterans | n = 181,093 | ICD-9 Clinical Modification | PTSD | Department of Veteran's Affairs | HR: 2.31 (95% CI: 2.24-2.39) |
| | | 55 years & over | | | | | |

Table Three: Types of Dementia explored in Included Papers

| | Byers et al. 2014 | Dent et al. 1998 | Mawanda et al. 2017 | Meziab et al. 2014 | Qureshi et al. 2010 | Yaffe et al. 2010 |
|---|-------------------|------------------|---------------------|--------------------|---------------------|-------------------|
| Alzheimer's Disease | | | | | | |
| Vascular Dementia | | | | | | |
| Lewy Body Dementia | | | | | | |
| Frontotemporal Dementia | | | | | | |
| Senile Dementia | | | | | | |
| Dementia not otherwise specified | | | | | | |
| Alcohol induced Dementia | | | | | | |
| Drug induced Dementia | | | | | | |
| Parkinsons | | | | | | |
| Other degenerative diseases of the basal ganglia | | | | | | |
| Dementia due to Huntingtons disease | | | | | | |
| Dementia due to Jakob-Creutzfeldt disease | | | | | | |
| Dementia due to Multifocal leukoencephalopathy (Encephalitis) | | | | | | |
| Dementia in conditions classified elsewhere e.g. physical condition | | | | | | |

The majority of papers focused on the four most common types of dementia, as illustrated in Table One, as well as a more generic dementia category (Byers *et al.*, 2012, Mawanda *et al.*, 2017, Meziab *et al.*, 2014, Yaffe *et al.*, 2010). Qureshi *et al.* (2010) provide the most comprehensive categorisation of dementia covering a far broader range of dementia types than the other studies reviewed (Table Three).

3. Findings

3.1 Dementia and MDD

Byers *et al.* (2012) explored both MDD and dysthymia, which they defined as a depressive spectrum diagnosis, in veterans with no evidence of dementia at a study baseline point between 1997 and 2000 (n=281,540). At a follow up point between 2001 and 2007, after adjusting for demographics and comorbidities, veterans diagnosed with dysthymia or MDD were twice as likely to develop dementia compared with those with no dysthymia or MDD (Byers *et al.*, 2012). The research of Byers *et al.* (2012) provides evidence for an association between the larger spectrum of depressive disorders and an increased risk of dementia in older veterans.

Dent *et al.* (1998) also explored the relationship between MDD and dementia, as well as investigating lower levels of depressive symptoms and cognitive decline. Veterans from World War II, living in Sydney, were tested in 1982 and again in a follow up session in 1991 (n=209). The results of the study found that the association between depressive symptoms and poor cognitive performance could be explained by the impact of verbal intelligence, a measure deemed resistant to the effects of brain pathology. Although a small correlation was found between MDD in 1982 and dementia in 1991, this was not statistically significant ($r=0.13$, CI: 0.00-0.26) and no concurrent correlation was found between MDD in 1991 and dementia in 1991. The lack of a significant difference in the prevalence of dementia in those with and without MDD at baseline led the authors to conclude that MDD was not a predictor of dementia (Dent *et al.*, 1998).

3.2 Dementia and PTSD

Exploring the relationship between PTSD and dementia Yaffe *et al.* (2010) found that US veterans (n=181,093) with a diagnosis of PTSD at baseline were significantly more likely to have a diagnosis of dementia at a follow up period (roughly seven years later), than those without a diagnosis of PTSD.

Qureshi *et al.* (2010) explored the association between dementia and PTSD in US veterans over the age of 65 (n=10,481). Four groups of participants were identified: 1) a control group, 2) a group with a PTSD diagnosis 3) a group with a Purple Heart (a medal presented to veterans physically wounded in combat which they used as a proxy for combat exposure) and 4) a group with both PTSD and a Purple Heart. Veterans with PTSD and no Purple Heart were twice as likely as those without PTSD and no Purple Heart, or those without PTSD and a Purple Heart to develop dementia. This study allows the distinction to be made between the impact of combat exposure and PTSD, showing PTSD to represent the more substantial risk for dementia (Qureshi *et al.*, 2010).

Meziab *et al.* (2014) investigated the relationship between PTSD and dementia as well as the impact Prisoner Of War (POW) status may have on this relationship (n=484). Adjusting for demographics, medical and psychiatric comorbidities, period of service, and the competing risk of death, there was an increased risk of more than 50% for dementia in POWs, an increased risk of more than 50% for dementia in those with PTSD and those veterans with both PTSD and POW status were twice as likely to develop dementia (Meziab *et al.*, 2014). Meziab *et al.* (2014) suggest that the additive effect of PTSD and POW status found in their study may indicate that the underlying mechanisms behind the impact of each status on dementia are different, presenting POW status as an additional risk factor pertinent to the veteran community.

Mawanda *et al.* (2017) examined the association between PTSD and dementia, as well as the potential impact of psychotropic medication use on this relationship in US veterans (n=417,172). Those veterans with a diagnosis of PTSD at baseline (2002-2003) were significantly more likely to have a diagnosis of dementia during the follow up period (2004-2012) (Mawanda *et al.*, 2017). The authors found that psychotropic medication use impacted this association, specifically those

veterans with a diagnosis of PTSD and a history of specific psychotropic medication use (SSRIs, Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs), and atypical antipsychotics (AAs)) were significantly more at risk of dementia than those with a diagnosis of PTSD and no history of psychotropic medication use (Mawanda *et al.*, 2017). In addition to this Mawanda *et al.* (2017) found that use of specific psychotropic medication at baseline (benzodiazepines (BZAs) or SNRIs) lead to a significantly increased risk of dementia at follow up, independent of PTSD diagnosis. This suggests that use of specific psychotropic medications may act as an additional risk factor for dementia (Mawanda *et al.*, 2017).

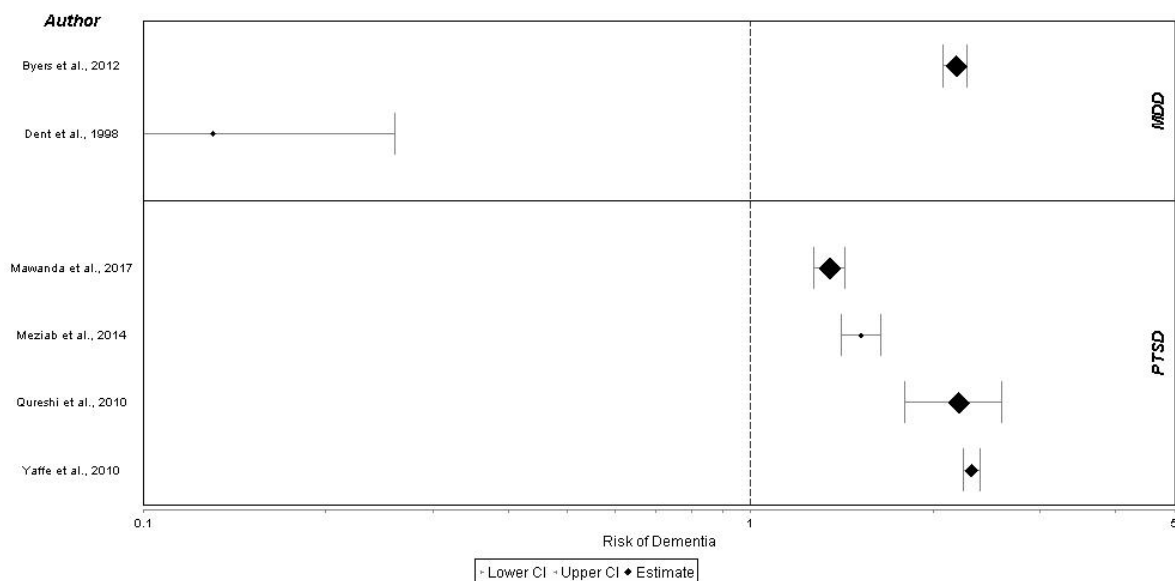


Figure Two: Forest Plot of MDD, PTSD and Dementia

As indicated in Figure Two the relationship between PTSD and dementia appears to be supported by the papers included in this review. Further research is required to ascertain the relationship between MDD and dementia and to understand the different results in the papers included in this review.

4. Discussion

4.1 Overview of Results

The review identified six papers which discussed either MDD or PTSD, and dementia in military veterans, published in peer reviewed journals. Despite the studied participants originating from the US or Australian military, given the neuro-biological nature of dementia, the results should hold relevance to the Armed Forces worldwide.

The initial hypothesis for this paper was that suffering MDD/ PTSD resulted in an increased risk of dementia in military veterans. This review found a significant association between PTSD and a later diagnosis of dementia which supports the assertion that a diagnosis of PTSD increases the risk of dementia in military veterans. The relationship between MDD and dementia illustrates conflicting results with one study supporting the relationship (Byers *et al.*, 2012) and another denying it (Dent *et al.*, 1998).

Dent *et al.* (1998) is the only paper which does not support the relationship between MDD/ PTSD and dementia. There are a number of potential reasons for this variation. The Dent *et al.* (1998) study is the only study which employs a prospective as opposed to retrospective design. Prospective

designs are thought to provide more accurate measures of risk, with less potential bias and confounding variables, so it may be that the non-significant relationship between MDD and dementia found in the Dent *et al.* (1998) study represents the more accurate finding. The Dent *et al.* (1998) study is also the only study that utilised clinical interviews to diagnose both MDD and dementia and thus its results may well be more valid than those drawing diagnoses from medical records. However, the Dent *et al.* (1998) study employed a comparatively small sample size of 209, compared to sample sizes in the 100,000s for the majority of the VA studies potentially impacting the power of its findings. The Dent *et al.* (1998) study is also the only study which was conducted outside of the US suggesting that there may be a cultural confounder at play, possibly in terms of the application of diagnostic criteria.

Within the civilian literature an odds ratio of between 1.90 (95% CI: 1.55 – 2.33) and 2.03 (95% CI: 1.73 -2.38) was identified in Ownby *et al.* (2006) meta-analyses for MDD and dementia. This is comparable to results of Byers *et al.* (2012) where a hazard ratio of 2.18 (95% CI: 2.08 – 2.28) was found. The outlier is Dent *et al.* (1998) study where no significant risk was identified.

4.2 Proposed explanations for findings

The research studies included in the review provided limited potential explanations for the mechanisms behind the association between MDD/ PTSD and dementia. Table Four below illustrates the pathways discussed within the papers.

Table Four: Neuro-biological Pathways

| Pathways | Paper | | | | | |
|-------------------------|-------------------|------------------|---------------------|--------------------|---------------------|-------------------|
| | Byers et al. 2012 | Dent et al. 1998 | Mawanda et al. 2017 | Meziab et al. 2014 | Qureshi et al. 2010 | Yaffe et al. 2010 |
| HPA: Cortisol | | | | | | |
| Cytokines: Inflammation | | | | | | |
| Aβ plaques | | | | | | |
| Cognitive Reserve | | | | | | |

Although there is limited discussion in the reviewed papers on the pathways that may link MDD/ PTSD and dementia, what discussion there is supports both the inflammatory neuro-degeneration hypothesis and the notion of brain reserve.

Evidence supporting both hypotheses is also present in the majority of papers included in the review. Byers *et al.* (2012) illustrate that dysthymia, as well as MDD, increases the risk of dementia. Mawanda *et al.* (2017) found that psychotropic medications also increase the risk of dementia. Since both dysthymia, and psychotropic medications, also impact neuro-inflammation this provides further support for the theory that inflammation is at the root of the association between MDD/ PTSD and dementia.

Additional risk factors that separately increase the risk of dementia in military veterans are found in three of the papers reviewed here. Meziab *et al.* (2014) conclude that POW status increases the risk of dementia, Mawanda *et al.* (2017) illustrate that psychotropic medications can increase the risk of dementia and Qureshi *et al.* (2010) show that Purple Heart status, indicative of combat exposure,

also increased the risk of dementia. Each of these additional risk factors supports the notion that dementia risk may steadily increase as each additional risk factor depletes individuals' brain reserve.

It could be assumed that from the plethora of additional risk factors the military veteran population face that their risk of dementia should be heightened over the civilian population. Although current rates of dementia in the military population appear to be no higher than the general population, at least with regard to the US military population (Sibener *et al.*, 2014), it would be expected that increasing rates of PTSD and MDD with recent deployments would lead to an increased 'future' rate of dementia in the future veteran population. In line with the work of Butters *et al.* (2008) it may be that each of these risk factors reduces the veterans' brain reserve, continuing to steadily increase their risk of dementia. If we take a similar stance then the risk for military veterans is not only dramatic but also highly complex. We suggest that future research should aim to unpack the pathways and mechanisms involved, as well as identify if and how these pathways are inter-related, in order to begin to understand the increased risk for this population.

4.3 Limitations

4.3.1 Retrospective Cohort Studies

The research presented here cannot identify causality; no conclusions can be drawn as to whether MDD and PTSD *cause* dementia or whether another factor causes both mental health conditions. As mentioned earlier, prospective studies are needed to provide more accurate measures of risk, with less potential bias and confounding variables.

4.3.2 Diagnostic Method Variability

As Meziab *et al.* (2014) highlight, studies that draw data from VA records draw from records kept for medical and billing purposes and as such may hold some misrepresentations. Dent *et al.* (1998) is the only study where the reader is provided details of how the diagnoses were made. As such we are unable to ascertain, but may assume, that there is a degree of diagnostic method variability between the studies, at least between the Dent *et al.* (1998) study and the VA studies.

4.3.3 Relevance to UK Military Veterans

The limited available evidence supports an association between PTSD and MDD with dementia within military veterans in the US. All of the retrospective cohort studies reviewed in this paper were based on data from the Department of Veteran's Affairs medical care system in the US and as such are limited to those who utilise this service (Byers *et al.*, 2012, Krishnan *et al.*, 2005, Meziab *et al.*, 2014, Qureshi *et al.*, 2010, Yaffe *et al.*, 2010). Such research may hold questionable salience in the UK where rates of mental health difficulties in military personnel vary substantially from the US. Empirical evidence exploring this association within UK military veterans, as well as the causal pathways underlying this relationship, is needed.

4.3.4 Potential Confounding Variables

Qureshi *et al.* (2010) also highlights that VA studies are unable to collect additional data that may have been influential, such as the duration, severity, or treatment of PTSD/ MDD which may have impacted the dementia diagnosis.

4.3.5 Lack of Neurological Data

The studies based on the VA were unable to collect any neurobiological information, such as inflammatory markers (Byers *et al.*, 2012, Krishnan *et al.*, 2005, Meziab *et al.*, 2014, Qureshi *et al.*, 2010, Yaffe *et al.*, 2010).

4.3.6 Systematic Review Process

Although a 10% sample of the abstracts for review were also screened by an independent author, the robustness of the review could have been improved if the entire review process was conducted by two independent authors.

4.4 Implications

4.4.1 Research Implications

We are still unable to prove, or explain, whether PTSD or MDD are risk factors for dementia within the UK, or worldwide, military veteran population. A large scale cohort study is needed to assess UK military veterans' MDD/ PTSD and dementia status over a significant period of time, including the capturing of neuro-biological markers and the use of brain imaging to understand the mechanisms underlying such an association. Such studies should be replicated to enable an appreciation of the risk to veterans worldwide. In addition to this further, small scale studies could be conducted to both measure neuro-biological markers and test the potential impact of additional risk factors on the prevalence of dementia.

4.4.2 Military Implications

It is understandable that much of the military mental ill-health research carried out to date is conducted with a focus on the here and now, and near future. However, the findings of this review supports taking a longer-term view, and the mental well-being of older veterans, especially in terms of dementia/Alzheimer's disease, should be considered. Whilst the onset of dementia cannot be currently predicted with any great accuracy (aside possibly from the genetic factors), nor the inevitable slow decline in cognitive functioning associated with the condition be alleviated, it may be possible to highlight veterans who may be at higher risk, and hence provide timely and measured support accordingly.

The evidence available to date which indicates that the veteran population is at heightened risk of developing dementia over the general population is highly relevant for the future care of military veterans. Should this potential increased risk be confirmed, then care provisions for veterans with dementia will need to be prioritised to some degree to ensure consistency with the Military covenant promise (Ministry of Defence, 2015). Further research is therefore required to identify whether the findings in this review of mainly US papers, hold true for UK veterans and indeed veterans worldwide.

4.4.3 Clinical Implications

The inflammatory neuro-degeneration hypothesis cites inflammation at the centre of the association between MDD/ PTSD and dementia. If proven this would have far-reaching clinical implications for the treatment of all three conditions. In addition to this anti-inflammatory medication may in fact help to mediate any potential relationship between conditions reducing the risk of dementia.

5. Conclusion

This review concludes that current evidence suggests that the military veteran community are at an increased risk of dementia due to the increased prevalence of mental health conditions such as PTSD and MDD within this population, as well as the supplementary impact of other military risk factors on this association. With the myriad of potential risk factors faced by military veterans it seems likely that the additive, complex interaction of all these factors impacts the development of dementia.

Both the theory of inflammatory neuro-degeneration and the brain reserve hypothesis hold potential in explaining this multifaceted relationship.

Financial support

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Conflict of interest

None

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